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The *ADAMTS1* Gene Is Associated with Familial Mandibular Prognathism

X. Guan[1], Y. Song[1], J. Ott[2], Y. Zhang[1], C. Li[1], T. Xin[1], Z. Li[3], Y. Gan[4], J. Li[1], S. Zhou[1], and Y. Zhou[5]

Abstract

Mandibular prognathism is a facial skeletal malocclusion. Until now, the genetic mechanism has been unclear. The goal of this study was to identify candidate genes or genomic regions directly associated with mandibular prognathism development, by employing whole genome sequencing. A large Chinese family was recruited, composed of 9 affected and 12 unaffected individuals, and the inheritance pattern of this family tends to be autosomal dominant. A single-nucleotide missense mutation in the *ADAMTS1* gene (c. 742I>T) was found to segregate in the family, given that the affected individuals must be heterozygous for the mutation. For mutation validation, we screened this candidate mutation and 15 tag single-nucleotide polymorphisms in the coding sequence of *ADAMTS1* among 230 unrelated cases and 196 unrelated controls using Sequenom Massarray and found that 3 in 230 cases carried this mutation and none of the controls did. Final results suggested that 2 single-nucleotide polymorphisms (rs2738, rs229038) of *ADAMTS1* were significantly associated with mandibular prognathism.

Keywords: whole genome analysis, SNV, craniofacial biology/genetics, orthodontic(s), molecular genetics, bioinformatics

Introduction

In a normal facial skeletal relationship, the upper jaw is in a more anterior position than the lower jaw, which is defined as skeletal class I jaw relationship and results in a normal bite and aesthetic facial appearance. Mandibular prognathism (MP; OMIM:176700; Online Mendelian Inheritance of Man, http://omim.org/entry/176700) is a dentofacial deformity, which is characterized by overgrowth of the lower jaw with or without undergrowth of the upper jaw. It leads to more prominence in the lower jaw than the upper jaw and a frontal teeth negative overjet (van Vuuren 1991). The unpleasant facial profile due to MP may decrease patients' self-confidence in social life and may lead to a severe psychological handicap. The lower anterior teeth cannot bite with upper teeth, leading to low masticatory efficiency (English et al. 2002), which may result in digestive disorders and compromised nutritional status. The discrepancy between upper and lower jaw may also cause the deficiency in speech articulation. In most cases, there is no abnormal finding in early childhood. However, with the growth of the general skeleton, inappropriate developments of upper and lower jaw emerge gradually and accelerate in puberty (Shira and Neuner 1976). The combination of orthognathic surgery and orthodontic treatment is needed for patients with severe MP to correct upper and lower jaw discrepancies. The prevalence of MP is much higher in Asian populations (2.1% to 19.9%), especially in Chinese and Japanese, than in Caucasian populations (0.48% to 4.3%; Fukui et al. 1989; Tang 1994; Coltman et al. 2000; Danaie et al. 2006; Perillo et al. 2010). The trait can occur in association with other systematic disorders, such as Apert syndrome and Crouzon syndrome, but we focus on nonsyndromic MP in this study.

MP is a disorder of bone development, and as indicated by familial recurrence and ethnic aggregation, a genetic component plays an important role in its etiology. The most famous example is the Habsburg jaw in the Spanish Royal family, in which MP was transmitted through many generations of the

[1]Department of Orthodontics, Peking University School and Hospital of Stomatology, Beijing, P.R. China
[2]Department of Laboratory of Statistical Genetics, Institute of Psychology, Chinese Academy of Sciences, Beijing, P.R. China, and Rockefeller University, New York, NY, USA
[3]Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology. Beijing, P.R. China
[4]Department of Laboratory of Molecular Biology and Center for TMD and Orofacial Pain, Peking University School and Hospital of Stomatology. Beijing, P.R. China
[5]Department of Orthodontics, Center for Craniofacial Stem Cell Research, Regeneration, and Translational Medicine, Peking University School and Hospital of Stomatology, Beijing, P.R. China

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Corresponding Author:
Y. Zhou, Department of Orthodontics, Center for Craniofacial Stem Cell Research, Regeneration, and Translational Medicine, Peking University School and Hospital of Stomatology, #22 Zhongguancun Nandajie, Haidian District, Beijing, 100081. P.R. China.
Email: yanhengzhou@vip.163.com

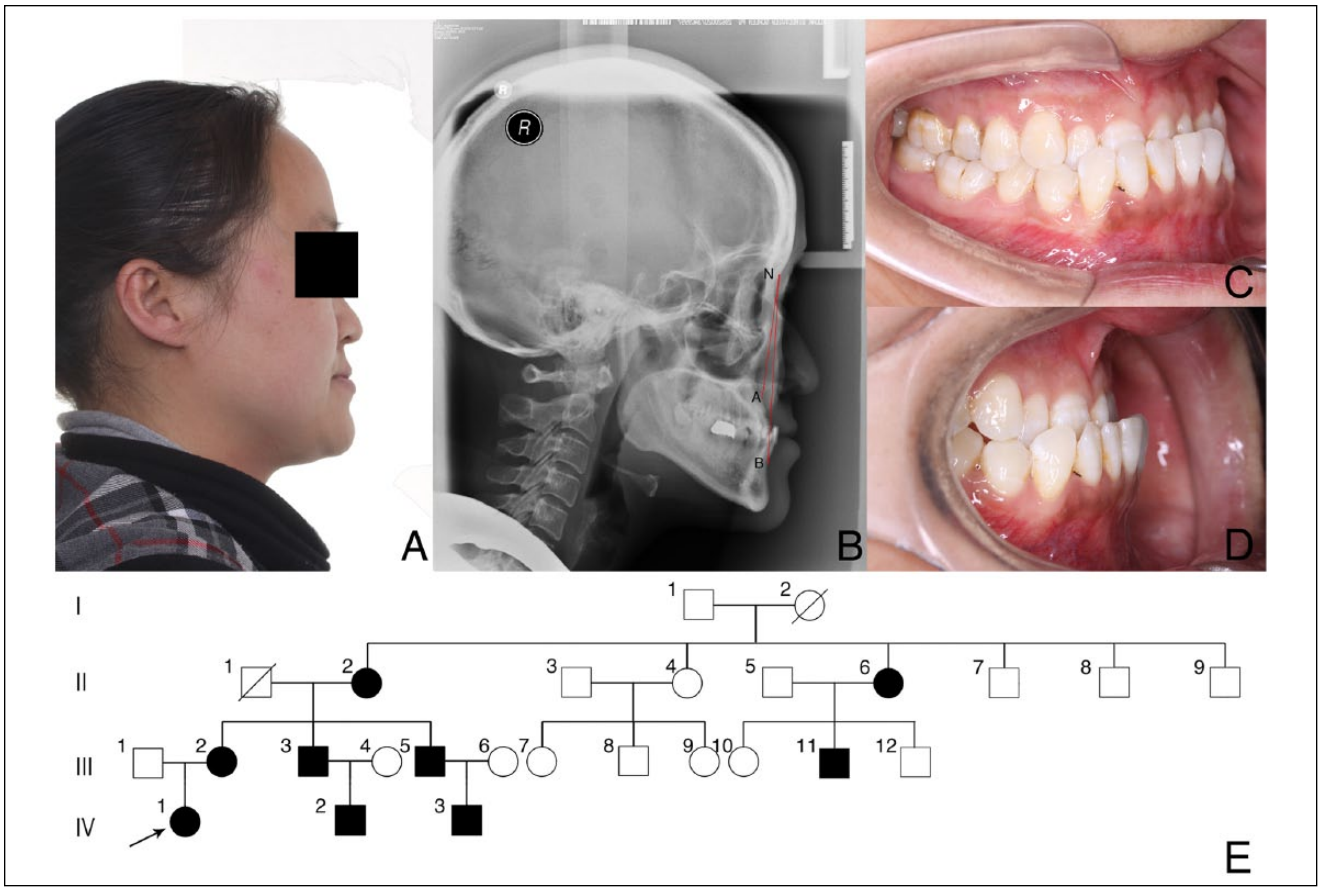

Figure. The characteristic records of a patient with mandibular prognathism (MP) and the pedigree chart of the MP family, (**A**) The facial lateral photograph showing a concave facial profile of an MP patient. (**B**) The cephalometric radiography of the same patient shows the lower jaw being in an anterior position of the upper jaw. A, subspinale, point of maximum concavity on maxillary alveolus; B, supramentale, point of maximum concavity on mandibular alveolus; N, nasion, most anterior point on frontonasal suture. A negative ANB angle indicates that the maxilla is positioned posteriorly relative to the mandible. (**C**, **D**) The intraoral photographs show an anterior teeth crossbite and a mesial molar relationship. (**E**) The Chinese family recruited in our study is composed of 9 affected and 12 unaffected individuals; the arrow indicates proband.

Habsburg line as a dominant trait with incomplete penetrance, which is the most common inheritance pattern of MP (McCullar 1992). However, the molecular genetic basis of this disease remains poorly understood. Genome-wide linkage analyses of MP have been carried out in Korean, Japanese, and Chinese patients and have identified several putative chromosomal loci for MP, including 1p36, 6q25, 19p13.2, 1p22.1, 3q26.2, 11q22, 12q13.13, 12q23, 14q24.3-31.2, and 4p16.1. Candidate genes within these loci include *IGF, TGFB3, HOXC, COL2A1*, and *LTBP2* (Xue et al. 2010; Li et al. 2011), and some of them have been identified to play important roles in bone development and metabolism. The inconsistent results of these genome-wide linkage analyses in different ethnic groups indicate that the causative gene of MP may not be unique. Furthermore, the molecular regulation mechanism of jaw development is not fully understood. Therefore, better understanding the genetic basis of MP can help us in terms of not only estimating susceptibility to this malformation but also better comprehending the molecular mechanism of jaw development.

The goal of the present study was to identify candidate genes or genomic regions directly associated to MP development, by employing whole genome sequencing of 2 affected individuals from a large Chinese family and a case-control study.

Methods

Family Recruitment

The Chinese family recruited in our study is composed of 9 affected and 12 unaffected individuals (Fig. E), with ages ranging from 12 to 67 y. All affected individuals have concave facial lateral profile, anterior teeth crossbite, class III molar relationship, and minus ANB angle (Fig. B). The protocols for this study and participant consent were reviewed and approved by the Institutional Ethics Committee at Peking University School of Stomatology.

MP diagnosis was based on patients' facial lateral profile, anterior teeth overjet, molar relationship, and data from cephalometric analysis. Cephalograms, study models, and bite registrations were taken from all 21 participants. The lateral cephalometric radiographs were taken in a natural head position with maximum contacted intercuspal occlusion. The

digital films were immediately uploaded to a radiographic database. A computer-based cephalometric and metacarpal-phalange length appraisal was developed with Dolphin Imaging 9.0 (Dolphin Imaging Systems, Chatsworth, CA, USA). The diagnosis criteria were as follows: presence of a concave facial lateral profile, anterior teeth crossbite, a class III molar relationship, and an ANB angle <0.0 degrees (Fig. B). There is no other symptom shared by the patients or unaffected individuals.

For further validation of findings, a case-control study was performed. For this purpose, 230 unrelated MP patients and 196 unrelated 120 controls (class I jaw relationship) were analyzed. The diagnosis criteria of MP patients were used as mentioned before. The diagnosis criteria of control patients were as follows: presence of a straight facial lateral profile, normal anterior teeth overbite and overjet, a class I molar relationship, and an ANB angle from 0 to 5 degrees.

We performed whole genome sequencing on 2 distantly related affected individuals with the most severe phenotype (individuals IV-1 and III-11 in Fig. E).

Whole Genome Sequencing

Genomic DNA was extracted from peripheral blood lymphocytes using the QIAmp Blood mini kit (Qiagen, Venlo, the Netherlands), and 1.5 μg of DNA from each individual was used for construction of the sequencing library with insert sizes of about 500 base pairs (bp). The whole genome of 2 affected individuals with MP in the Chinese family was sequenced by pair-end sequencing, which was performed on an Illumina HiSeq 2000 platform (Illumina, San Diego, CA, USA) (Bentley et al. 2008). Shorter reads (reads <76 bp) resulted in ambiguous alignments, which can be regarded as unquantified and discarded from whole data. The sequencing reads were mapped to the reference human genome (GRCh37.5).

Variant Calling

Single-nucleotide polymorphism (SNP) calling was done by the Sequence Alignment/Map tools (SAMtools 1.7) and Genome Analysis Toolkit (GATK 1.0.5083) and then filtered by dbSNP135 and the 1000 Genome Projects database. Ensemble and SIFT predictions were performed to estimate the function of all the single-nucleotide variants. Calling for short coding insertions or deletions (indels) was done by GATK only, and structural variants—including long deletions (>60 bp), tandem duplications, long insertions, inversions, and replacements—were called by Pindel (Appendix Fig.).

Mutation Validation

Sequenom mass array was used to confirm the presence of variants identified via whole genome sequencing in the Chinese family and in the case-control study. Haploview 4.2 software was employed to construct haplotypes of candidate gene. The Sequenom MassARRAY system is a DNA analysis platform that efficiently and precisely measures the amount of genetic target material and/or variations and is suitable for a variety of research applications, including somatic mutation profiling, genotyping, methylation analysis, molecular typing, and quantitative gene expression. Detection by MALDI-TOF mass spectrometry offers high sensitivity and accuracy. Chi-square or Fisher exact calculations were used to assess Hardy-Weinberg equilibrium and significance in genotype- and allele-type frequencies between the case and control groups. A P value <0.05 was considered statistically significant.

Quality Control

The first quality check measure was based on read length, and reads <76 bp were regarded as unquantified. Furthermore, we also employed coverage percentage as a quality check measure to increase reliability in whole genome sequencing, and the coverage of the 2 individuals in the MP family were 92.4% and 91.8%. Therefore, the filtering reads of whole genome sequencing were considered reliable.

Results

Whole Genome Sequencing and Mendelian Linkage Analysis Identified a Candidate Single-nucleotide Missense Mutation for MP

A mean 88-Gb sequence was generated per affected individual as pair-end 76-bp reads in 2 affected individuals with MP. After discarding low-quality reads, we achieved ~30-fold coverage of the genome. SNP calling based on SAMtools gave us 3,435,919 and 3,450,352 SNPs, respectively, for affected individuals IV-1 and III-11 (Fig. E). After filtering for the known SNPs and SNVs (single-nucleotide variants) using dbSNP135 and the 1000 Genome Projects database, we found 83 nonsynonymous and 2 splice site mutations shared by the 2 affected individuals of the Chinese family (Appendix Fig.).

This pipeline was repeated using the GATK and 3,511,134 and 3,519,355 SNPs, respectively, for affected individuals IV-1 and III-11 (Fig. E). Following the same filtering steps as above, the 2 individuals shared 53 nonsynonymous SNVs and 5 splice site mutations.

Ensemble and SIFT predictions were performed to estimate the function of these variants. We focused on those mutations, which could probably damage the protein structure under Ensemble or SIFT prediction, and finally chose 65 candidate SNVs (Appendix Table 1), which are distributed in different genes to analyze Mendelian linkage among 21 members in this family using Sequenom Massarray. As a result, we found 1 novel SNV (chromosome 21, 28210577, 1, T/C), which was predicted to have damaging influence to *ADAMTS1* and was strongly linked with the disease. In total, 10 individuals with the same mutations in the *ADAMTS1* gene were found in the family, 9 of whom present the MP phenotype; that is, there is 1 exceptional individual who carries the causal mutation but is unaffected.

Haploview 4.2 software was employed to construct haplotypes of *ADAMTS1*, with the restrictive standards including r^2 value >0.8 and minimum allele frequency >0.05, and all the tag SNPs in the gene were determined. After function analysis, 15 tag SNPs in the *ADAMTS1* gene—besides the mutation observed in the Chinese family—were selected for genotyping, which included as much functional SNPs as possible (Appendix Table 2). We found that 3 in 230 cases carried the mutation obtained from the MP family and none of the controls did. The chi-square test was used to compare differences in genotype and allele frequencies between the case and control groups. All markers were in Hardy-Weinberg equilibrium in both class I and MP groups. Two SNPs in *ADAMTS1*, rs2738 and rs229038, were found to be significantly associated with MP (P = 0.001 and P = 0.019, respectively; Table and Appendix Table 3).

No Indel Is Strongly Related to MP Deformity

Indel calling was done by GATK and then filtered by dbSNP135 and the 1000 Genome Projects database. The intersection indels in the coding sequence of the 2 siblings were used for Mendelian analysis; 46 indels were used, but none of them showed a strong relationship with MP.

Table. MP and Class I Groups: Number of Subjects with Each Genotype and Number of Alleles Found in Each Group (*ADAMTS1* Gene).

	Subjects, *n*	
SNP: Genotype	MP	Class I
rs2738		
AA	3	5
CC	180	119
AC	47	71
P = 0.001		
rs229038		
CC	39	48
GG	87	51
CG	102	96
P = 0.019		
SNP: Allele	Alleles, *n*	
rs2738		
A	53	81
C	407	309
P = 0.000		
rs229038		
C	190	192
G	266	198
P = 0.028		

MP, mandibular prognathism; SNP, single-nucleotide polymorphism.

Discussion

MP is a bone development disorder. The pattern of bone formation in the mandible includes intramembranous ossification and endochondral ossification, with only intramembranous ossification in the maxilla (Iwata et al. 2010). Maxilla and mandible are both derived from the first branchial arch (Cobourne and Sharpe 2003). The mandible is ossified in the fibrous membrane covering the outer surfaces of Meckel cartilages (Shibata and Yokohama-Tamaki 2008). These cartilages form the cartilaginous bar of the mandibular arch. In the seventh week of embryonic development, the mesenchymal cells aggregate in the region of the mental foramen (an anatomic structure of the mandible) and then differentiate to osteocytes, followed by bone matrix formation and ossification, called the mandibular corpus ossification center (Wyganowska-Swiatkowska and Przystanska 2011). In the 13th week of embryonic development, the condylar cartilage merges with the mandibular corpus ossification center to form the mandible (Orliaguet et al. 1993). The condylar cartilage forms the condyle through endochondral ossification. Before 1 y after birth, mandibular development in the sagittal direction occurs due to the continuous ossification in symphysial fibrocartilage, and bone resorption and deposition occur in the anterior and posterior borders of the ramus. MP is mainly due to the overgrowth of the mandible in the sagittal direction (Chang et al. 2006). However, there is no abnormal finding in early childhood. With the growth of the general skeleton, inappropriate developments of upper and lower jaw emerge gradually and clearly accelerate in puberty (Noble et al. 2007). Therefore, abnormal bone remodeling in adolescence may be responsible for the occurrence of MP.

There are several subtypes of MP, such as mandibular overgrowth with or without maxillary retrusion. Since there is extensive clinical heterogeneity, the genetic bases of types of MP may be different (Xue et al. 2010; Li et al. 2011). There are many genes known to be involved in the process of mandibular development; however, the mechanism of gene regulation leading to mandibular overgrowth is still not clear.

Whole genome sequencing is a powerful tool to explore the causal variants of genetic disorders. Compared with genome-wide association studies, whole genome sequencing is optimized to detect the role of causal variants in small samples. In this study, we chose 1 pedigree to investigate the genetic mechanism of MP. The clinical features of all patients are similar, including maxillary deficiency and MP; therefore, the clinical heterogeneity is minimal. According to the pedigree, there is no difference in the number of male and female affected by MP, and the inheritance pattern of this family tends to be autosomal dominant. To eliminate background gene variants, we chose 2 distantly related affected individuals and then performed whole genome sequencing. Although MP has a relative high prevalence, we try to disregard common variants found in the dbSNP135 and 1000 Genome Projects databases because rare large-effect mutations are now recognized as causes of many common medical conditions (McClellan and King 2010). Therefore, a pipeline was subsequently developed to recover rare variants (i.e., absent or <1% frequency between 2 databases), for which the affected individuals should be heterozygous. If unsuccessful, we would turn to more common variants. Fortunately, we found 1 rare variant segregating in the family.

Combined with linkage analysis, a nonsynonymous single-nucleotide mutation (c. 742I>T) in *ADAMTS1* was the only putative causative variant in all cases. With 1 exception, none of the unaffected individuals carry the mutation in the *ADAMTS1* gene. The single unaffected individual with the mutation has a straight facial lateral profile; however, the position of the lower anterior teeth presents a little bit forward, which is caused by mandibular overgrowth. This indicates incomplete penetrance, which has been suggested in other studies (El-Gheriani et al. 2003).

The damaging effects of *ADAMTS1* mutations (c. 742I>T) reported in this study are the first to be described in a jaw developmental disorder. ADAMTS—a disintegrin and metalloprotease with thrombospondin type I motifs—is a family of extracellular proteases (Apte 2009). The function of ADAMTS is to cleave proteoglycans, such as aggrecan, versican, and brevican, which has been shown to be involved in various human biological processes (normal or pathologic), including connective tissue structure, cancer, coagulation, arthritis, angiogenesis, cell migration, and bone development (Beristain et al. 2011; Stanton et al. 2011; Kumar et al. 2012). *ADAMTS1* is the first member of the ADAMTS protein family that is involved in proteolytic modification of cell surface proteins and extracellular matrices (Rehn et al. 2007). The unique structure of *ADAMTS1*, characterized by the presence of thrombospondin type I motifs, is shared by other newly identified proteins in mammals and in *Caenorhabditis elegans*, which constitute the ADAMTS subfamily that may perform well-conserved biological functions (Shindo et al. 2000). *ADAMTS1* is anchored to the extracellular matrix by an interaction between its carboxyl-terminal spacing region with its thrombospondin type I motifs and sulfated glycosaminoglycans, such as heparan sulfate (Kuno and Matsushima 1998). Therefore, *ADAMTS1* may serve as a local factor processing as-yet-unknown substrates by protease activity.

It has been reported that *ADAMTS1* is expressed in the rat mandible during embryonal and early postnatal stages (Mitani et al. 2006). *ADAMTS1* is also expressed in teeth during eruption (Sone et al. 2005). Some studies have suggested that *ADAMTS1* may play an important role in bone growth, and the deletion of *ADAMTS1* would result in development retardation (Lind et al. 2005). *ADAMTS1–/–* mice were significantly smaller than wild-type mice; the reduction in bone growth was already significant at birth and was accentuated thereafter. Furthermore, structural abnormalities of adrenal glandular tissue were found in *ADAMTS1–/–* mice, and only a few capillaries containing blood cells were observed in the adrenal medulla (Shindo et al. 2000). Although the deletion of *ADAMTS1* could lead to bone growth retardation, interestingly, overexpression of *ADAMTS1* reveals an effect on bone mineral density in transgenic mice (Hu et al. 2012). These studies suggest that *ADAMTS1* may play a potent regulatory role during bone remodeling. Therefore, the inactivating mutation in *ADAMTS1* may disrupt the balance of upper and lower jaw bone growth and then lead to abnormal mandibular development and MP. However, we need advanced research to determine why the phenotype of *ADAMTS1* mutation manifests as mandibular overgrowth and maxillary hypoplasia.

The result of mutation validation in unrelated MP patients indicates that the mutation in *ADAMTS1* can explain only a small part of MP occurrence in the Chinese population. Moreover, *ADAMTS1* was not identified in previous genome-wide association studies. This suggests that *ADAMTS1* is not the only causative gene of MP, which is coincident with conclusions in previous studies indicating that MP is a polygenetic disorder (Cruz et al. 2008). Thus, locus and allele heterogeneity is expected for MP, including differences in the causative gene/alleles among different ethnic groups, populations, and even families. Therefore, there is so much remaining work to do for a comprehensive understanding of the genetic outline of MP.

In summary, we performed whole genome sequencing and linkage analysis with an MP family and found that 1 nonsynonymous single-nucleotide mutation (c. 742I>T) in *ADAMTS1* was the only affected variant in all cases, indicating that *ADAMTS1* is the causative gene in this pedigree. We validated the mutation with 230 unrelated MP patients and 196 controls and found that 3 cases carried this mutation and none of the controls did. Here, we present the first report of *ADAMTS1* as a causative gene of familial MP. It is more important that our finding first focused on 1 nonsynonymous single-nucleotide mutation (c. 742I>T) associated with dominant inherited MP. Functional studies of *ADAMTS1* in bone development are necessary to better understand the etiology of MP.

Author Contributions

X. Guan, Y. Song, Y. Zhou, contributed to conception, design, data acquisition, analysis and interpretation, drafted the manuscript; J. Ott, Y. Zhang, C. Li, T. Xin, Z. Li, Y. Gan, J. Li, S. Zhou, contributed to conception and data analysis, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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